A CHEMICAL HYPOTHESIS FOR THE ETIOLOGY OF CANCER.[1]

BY JOHN ROGERS, JR., M.D.,
OF NEW YORK,
Visiting Surgeon, Gouverneur Hospital; Assistant Visiting Surgeon, St. Francis Hospital.

In all the vast literature upon the etiology of cancer, little or nothing has been contributed towards the possibilities of its chemical or chemico-biological origin. Before anything was known of parasitology, Sir James Paget expressed his belief in both a local and constitutional cause; but such terms were very vague then, though now with the recent discovery of the almost universal presence of enzymes in living tissue, and with the added facts supplied by the chemistry of the blood, a reasonable working hypothesis can be constructed. And it is the more worthy of study in that, in spite of all the great labor which has been expended in the search for a bacterial origin of the disease, the net result at present seems to be a verdict of at least "not proven." Even now the pathological chemistry of the blood is still in its infancy, although to it is ascribable the ultimate cause of all deaths. In those due to bacteria this chemistry seems almost hopelessly complex; but there are a very large class of disorders, notably those of which arterial sclerosis is a type, which to be sure seem equally little understood, but which ought to be more accessible to the test-tube. These, which can perhaps properly be called the chemical disorders of advancing life, are often associated with cancer, and any study of the chemical constitution of the blood in the latter condition should shed some light upon the other very common derangements. The simpler elements and compounds have been pretty thoroughly investigated with a general negative result, but the more com-

[1] Read before the New York Surgical Society, April 22, 1903.

plex organic bodies, like the carbohydrates and proteids, have scarcely been considered, and it is to them I wish to call attention.

In the last United States Census Report the greatest increase in mortality is shown to be in nephritis, apoplexy, influenza, cancer, old age, and heart disease. With the exception of influenza, and for the present of cancer, all the rest may be said to belong to the connective-tissue degenerations, an evident disorder of metabolism which is universally ascribed to some "irritant" circulating in the blood. But, so far as I know, the exact character of this irritant or blood derangement has not been determined; and, indeed, its actual nature seems only inferred from the similar changes produced by bacterial and other poisons. That it is chemical seems, however, admissible, if only from the very close analogies with the pathological findings in chronic alcoholism. Granted so much, and we come immediately to diet and mode of life, which are universally conceded to be intimately connected with every disease, but chiefly with disorders of metabolism, that is those which are purely chemical. This group of diseases, so prominent in the census report, accompanies general prosperity, wealth, good and easy or strenuous living, with its nervous strain and interference with proper assimilation, oxidation, and excretion. The association is not as problematical as might at first sight appear, as it emphasizes the chemical nature of the problem involved, and cancer is constantly appearing under such conditions. It seems most common in the well-to-do, the well-fed, and the sedentary, and attention has frequently been called to its connection in the same sense with gall-stones. The statistics compiled to show infected localities and houses, though intended to bring out the possible bacterial origin, have always seemed to me equally applicable to diet and mode of life, for low-lying rich soils along river bottoms are more productive and give greater creature comforts and ease than hill-sides and rocky soils. That certain dwellings or families suffer more than others speaks no more for contagion than it does for cerebral hæmorrhage or

senility. The inhabitants may prefer or be forced to live in the same way. Heredity, an exceedingly vague and uncertain matter by the way, though estimated as traceable in from 10 to 35 per cent. of all cases of cancer, has about an equal significance. There is also a somewhat apparent parallel in the occurrence of goitre in certain regions and peoples. All that is known about these factors points towards a chemical influence. The Teutonic and allied races are notoriously subject to malignant disease, and the sufferers from the malady have always seemed to me to present many close analogies to the well-to-do of other races. They are generally well nourished and fond of eating and alcoholic drinks, and are more or less sedentary and phlegmatic in their habits. In the lower animals cancer seems to be unknown below the mammalia, and of these the carnivora, and particularly the omnivora, are much more subject to it than the herbivora, and apparently the more highly-bred and domesticated the animal the more apt it is to be attacked by cancer.[1, 2, 3] These facts taken singly would have little significance, but grouped together and considered with the practical disproof of the parasitic theory, they are very suggestive. The means other than operative which have been found capable of ameliorating or curing cancer in a few undoubted instances can all be considered chemical in their nature and acting through the blood. The successes in the treatment of sarcoma by the injection of the erysipelas or mixed toxins can only be thus interpreted. To be sure, this is generally considered as evidence of the bacterial nature of the affection; but there is no other proof than analogy, and the cure, though evidently chemical, may be susceptible of a simpler explanation than Ehrlich's theories of the mechanism of immunity would indicate. A possible hint towards the solution is supplied by the fact that during infectious diseases the carbohydrates of the body, and particularly glycogen, are markedly decreased in amount.[4] The starvation of malignant tumors by cutting off their blood supply,[5] a method much advocated by a member of this society, seems to have considerable significance, especially when considered in relation

to the results obtained by thyroid feeding and oophorectomy. Oophorectomy in young animals, as is well known, has a pronounced influence on the development of the other sexual organs, and to a much less extent upon the whole organism. Certain experiments have proved that this is due to some internal secretion, probably an enzyme which is given off by the ovaries, and which, to insure normal growth, is evidently a necessary constituent of the blood.[6] Its effect is no more remarkable, of course, than that of the secretions of the thyroid gland and the suprarenal bodies, except in its selective influence upon the growth of certain organs and portions of the body. In other words, certain cells must require a particular kind of nutriment, or modification of the ordinary nutriment produced by the ovarian enzyme, in the blood. The endless attempts at inoculation by transplantation of cancerous tissue, to have any reasonable hopes of success, show that animals of the same species must be employed. The rarity of this success, however, might be inferred from the practically unknown inoculation of the operating surgeon, but auto-inoculation, even if it needed other demonstration than the occurrence of metastases or recurrence, is uniformly successful. A proper soil seems to be therefore a necessity, and this can be sought in nothing else than the constitution of the circulating blood, and I shall try to show that the carbohydrate group ought to be the first to be examined. In the first place, the recent discoveries as regards enzymes and their existence in all parts of the living body, and their necessity in metabolism, have already been referred to. Every tissue appears to assimilate its nutriment and to carry on its existence by means of its enzymes and the reversibility of their action.[7, 8, 9, 10] Only a few of these mysterious entities have as yet actually been proved capable of reconstructing the complex organic bodies from the simpler soluble and diffusible substances into which, ever since the beginning of physiology, the digestive enzymes have been known to resolve such bodies. Nevertheless, there now appears to be no reasonable doubt but that this is the method by which all living matter exists. There are in general

the three main groups of enzymes,—the proteolytic, the amylolytic, and the lipolytic,—corresponding to the three main groups of food stuffs, to which must be added a fourth or oxidative enzyme. Each tissue possesses one or more of the enzymes of these groups, although each enzyme, according to its origin, exhibits some peculiarity or selective action. The proteolytic enzymes of the lung, for example, can digest insoluble lung proteids, while the similar enzymes derived from the liver cannot do so. The proteolytic enzymes of either lung or liver, however, can digest the albumoses obtained from lung proteids. The albumoses, by the way, are one of the first cleavage products of all proteid digestion.[11] Conversely, it is presumable that, like lipase, which reconstructs fat from fatty acids and glycerin, lung tissue can only be kept in repair by its own enzyme. It has been known for some time that cancerous tissue contained enzymes, but I am indebted to some as yet unpublished researches of Dr. Buxton, at the Cornell Medical College, for the knowledge that the most abundant and constant enzyme present is amylolitic. He will not affirm that its amount is directly proportionate to the malignancy of the tumor, though, from what is known of the ordinary digestive enzymes, which vary according to the work they are required to perform, this seems possible of inference. However this may be, glycogen, which is the animal equivalent of starch, is found in all tumors in a quantity varying directly with the malignancy of the disease.[12, 13, 14, 15] It is a colloidal, non-diffusible body, and its presence in the cells can only be explained by virtue of the enzymes they are known to contain.

There remains now the adjustment of the details of this hypothesis for the local and constitutional origin of cancer to the clinical facts, and the means of proving it. The individual cells of a malignant growth bear a very close resemblance to the fœtal embryonic type, and are notoriously hard to differentiate from those of granulation tissue. Both fœtal and granulation tissues are also peculiar in being rich in glycogen, which gives the first suggestion for approaching the problem, and from Dr. Buxton's work I know that granulation

tissue contains considerable amylase. Traumatism in one form or other is universally accepted as about the only apparent constant cause of cancer, and it is always accompanied by more or less of an attempt at repair by granulations or an infiltration of embryonic round cells. In constructing a hypothesis for the origin of cancer, it is not departing too much from the facts to affirm that these, by their enzyme, assimilate from the blood the carbohydrate to form the glycogen necessary for their life and growth, and by the excess of nutriment present and their own exuberant vitality in given instances proceed to outgrow their natural limits in the shape of malignancy. It is conceivable that ordinarily the residue of the original destruction (using the analogy of the lung and its proteolytic enzymes previously referred to) may supply the food required to start the reparative process, as the enzymes of each part have a selective action, and to complete their function seem to need a food represented in the body of the cells from which they are derived. Ordinarily, when this is exhausted, the enzymes of the surrounding tissues neutralize any excessive cellular reproduction and repair is natural. If there is an excess of food or of enzyme, however, malignant degeneration follows. The comparative rarity of the indefinite continuation of this reparative reproduction or its inception in some other way do not seem to me insurmountable obstacles to the theory suggested above. Adami has called attention to the need of a theory which will cover the cause of all tumors as their original source, and the lines differentiating the numerous growths and allied disorders are so indistinct as alone to show their relationship. The matter of age seems to have some bearing on the problem, and it is not so much the age of the patient as that of the particular organ attacked, for malignant disease is apt to affect those which have reached the limit of active growth. Sarcoma, for example, occurs in bones at the epiphyses as they become bony, and carcinoma in glands like the mamma at the menopause. That there is a "habit of growth" is merely a statement and not an explanation, and scarcely accounts for those cases which, according to Cohnheim's theory,

develop from misplaced embryonic cells or from benign embryonic tumors like the teratomata after they have remained dormant for a longer or shorter period. These misplaced "cell rests" appear to be common enough in the lower animals and give rise to no particular disturbance. That in man they should now and then produce malignant tumors is explainable on the hypothesis of the presence of a nutriment similar to that found in the fœtal environment of these cells and brought into existence by the diet or mode of life of the subject, or to an enzyme started into activity by some unnoticed injury, or to a combination of all these factors.

Some cases of sarcoma have recovered after operative removal, and yet more or less diseased tissue has been left behind. There are no similar records as regards carcinoma, although, at least, one well-authenticated case, apparently after existing some time, has recovered spontaneously. It is significant in that glandular tissue contains more enzymes than other structures, although they all contain some amylase. In other words, the cells of sarcoma belonging to the connective-tissue group have not the excessive energy in the shape of enzymes needed to maintain the malignancy of the original focus. On the other hand, some malignant growths recur worse than ever after operation. But following hæmorrhage, the blood is found experimentally to contain an increased quantity of sugar which might be supposed, for purposes of this hypothesis, to afford more nourishment to the disease; or, if this were untenable, the restraining effect of the normal surrounding enzymes might be conceived to be inhibited as a result of the general depression or shock of the interference. Their analogues, the digestive enzymes, are certainly disturbed under such conditions.

However fanciful some of these explanations may be regarded, they serve to indicate how the hypothesis of a combined local and constitutional cause of cancer can be made to apply to the numerous clinical observations. The apparent cures effected by the X-rays, for example, harmonize with this in that it is known that they have an inhibitive or in-

jurious effect upon many enzymes, and particularly upon diastase, a close relative of amylase.[16] The latter does not seem to have in itself been thus studied. To my mind, there is thus enough evidence to warrant a chemical investigation of the blood, and particularly of its carbohydrate constituents. The rarity of the simultaneous occurrence in the same subject of sarcoma and carcinoma might seem to complicate the study by suggesting the need of a search for two different substances, but with the many similarities in the age and general characteristics of the cells or tissue attacked, and the variations in the carbohydrates and local enzymes, it is not probable. The carbohydrate food stuffs as introduced into the alimentary tract, and from which the animal carbohydrates must be chiefly derived, include a large group of principles whose general formula can be represented as $(C_6(H_2O)_n)_{n^1}$, or six atoms of carbon united with a definite amount of water and the whole raised to the $_{n^1}$ power. This may be formed by the union of CO_2 plus H_2O, which equals CH_2O plus O_2, and subsequent polymerization, as $6(CH_2O)$ equals $C_6H_{12}O_6$, or as a cleavage product from proteid matter by enzymes. There are other theories, but these serve as simple examples. However produced, the carbohydrates are divided into three main groups, namely,

The amyloses or polysaccharides $(C_6H_{10}O_5)_n$, including cellulose, starch, and glycogen.

The saccharoses or dissaccharids $(C_{12}H_{22}O_{11})$, including maltose and cane sugar.

And the glucoses or monosaccharids $(C_6H_{12}O_6)$, including glucose and levulose.

The most convenient and reliable method of testing is by Fehling's solution, although the first two groups—the amyloses and saccharoses, to give the reaction—have first to be hydrated or inverted by boiling with acids. Superficially, the matter looks simple enough, but in the body there are some carbohydrates which are not thus easily capable of reducing copper. They often contain nitrogen, and are known as glycoproteids, of which mucin is an example. This body can be made to

yield a non-reducing carbohydrate, which by appropriate treatment can still be made into a cupric oxide reducing but non-fermentable sugar.[17] As mucin is so abundant a constituent, especially of the connective-tissue group of organs, and pathologically of many structures in myxœdema, between which and cancer numerous analogies have been drawn, the glycoproteids seem worthy of serious attention. In fact, some by-products I have obtained in the course of analyses are very suggestive in their physical properties of such a glycoproteid. I began examining the blood obtained during operations on cancer and other patients two years ago, and have particularly to thank Dr. Willy Meyer for many courtesies. The blood was received in absolute alcohol in a tall 100 cubic centimetres stoppered cylinder as it flowed from the wound. The exact quantity could thus be ascertained, and was preserved indefinitely by the alcohol, which at the same time presumably holds in solution all the glucose. It also precipitates proteids, together with the blood enzymes, which, even after months of preservation in alcohol, I have found capable of extraction from the precipitate by a 50 per cent. solution of glycerin and without alteration of their properties. The glycoproteids are also precipitated with the proteids, and among these bodies may be counted jecorin, a reducing substance said to be a compound of lecithin and a carbohydrate which is soluble in ether and in dilute but not in absolute alcohol.[18, 19, 20] The above brief *résumé* suggests various lines of procedure differing quite considerably in detail, but with the general object of isolating some carbohydrate which would be constant in cancer blood. My early results were somewhat variable, but seemed to warrant perseverance, and this winter, under the guidance of Dr. Wolf, the physiological chemist at the Cornell Medical College, the analyses were continued, using alcohol to receive and preserve the specimens as before. The specimens averaged from fifteen to twenty cubic centimetres of blood, and even a smaller amount than this I have found capable of very accurate manipulation. By Dr. Wolf's advice, the glucose, being the simplest to investigate of all the possible

carbohydrates, was chosen as the first line of research. The alcohol containing it in the cylinder was filtered, evaporated to dryness in vacuo to avoid hydrolysis, and the residue of this filtrate extracted with water. An opalescent mixture resulted, quite suggestive of glycogen in appearance, which gave a heavy precipitate by treatment with a few drops of concentrated HCl and phosphotungstic acid. The filtrates from this have shown a pretty constant amount of glucose in specimens which were taken from patients suffering from every kind of surgical disease and of all ages. This might seem disappointing, but as the only disease which seems to be incompatible with the coexistence of cancer, namely, diabetes, has an excess of glucose in the blood, it is reasonable to suppose that some other carbohydrate ought to be sought for. Nevertheless, with the improved technique suggested by Dr. Wolf, so few of my analyses have been completed, that I cannot speak as yet with any degree of positiveness. At the same time that glucose was sought in the alcoholic filtrate, the original proteid precipitate, after being thoroughly washed with alcohol and rubbed up with sand, was treated with twice the volume, of the recorded amount of the specimen, of a 50 per cent. glycerin and water solution. At the end of forty-eight to seventy-two hours a definite amount of this glycerin extract was tested for its amylolytic and glycolytic powers. It is worthy of note that the amylolytic blood enzymes seem quite variable in power in the different specimens. But as yet I can make no definite statements nor draw any conclusions upon this part of the work. It is evidently one, however, which must be thoroughly sifted. The glycolytic enzyme in the blood is much disputed by numerous competent observers. The sources of error are obvious in that glucose is a most fermentable product, and the slightest bacterial contamination would vitiate results. But from the gross appearance of the reduced copper, which is used to measure the action of the supposed glycolytic enzyme upon a definite quantity of glucose, my results have seemed to favor the theory of the presence in the blood of a marked glycolytic enzyme. The subjects which are at the same time the

simplest and the most necessary to clear up are the blood enzymes and their comparative vigor or abundance in all ages and kinds of disease as well as in health and the glucose which is always present to a certain extent. I have hitherto neglected the glycoproteids, notably, jecorin, and after the matter of the enzymes and the glucose has been determined this seems the next to be taken up, combined possibly with receiving the blood as shed in ether instead of alcohol. In examining the aqueous extract of the original alcoholic filtrate, the consideration of the carbohydrates, which are only detectable by Fehling's solution after inversion, forms an interesting problem, which I regret that as yet I can cast little light upon. These bodies consist of the amyloses and saccharoses, and should have a very important bearing on the problem, as I have found that they are present, but have not been able to demonstrate any characteristic relative quantitative amount.

The above brief sketch I trust will serve to show some reasons for approaching cancer from a new direction, and possibly induce some better equipped chemist to undertake what cannot be a profitless study, as to be of any value the blood must be examined in health and disease and at all ages, and a comparison then made. Clinically, it looks as though the result to be expected is a quantitative and not a qualitative change in the chemical constitution of the blood.

REFERENCES.

[1] Park. American Journal of the Medical Sciences, 1898, Vol. cxv, page 503.
[2] Marshall. Lancet, 1891, ii, p. 415.
[3] Beard. Lancet, 1902, i, p. 1759.
[4] Luschi. Jahrsb. Th., 1900, Vol. xxx, p. 449.
[5] Dawbarn. Reference Handbook of Medical Sciences.
[6] Nicholson. University of Pennsylvania Medical Bulletin, January, 1902, p. 401.
[7] Loewenhart. Chemical News, 1901, lxxxiii, Nos. 2150-55.
[8] American Journal of Physiology, 1902, vi, p. 331.
[9] Hill. Journal of the Chemical Society, 1898, lxxiii, p. 634.
[10] Schmiedeberg. Archiv für experimentale Pathologie und Pharmacologie, 1881, xiv, p. 379.

[11] Hofmeister's Beiträge für chemische Physiologie und Pathologie, 1903, iii, 446.
[12] Brault. Jahrsb. Th., 1897, xxvii, 753.
[13] Meillere and Loeper. Jahrsb. Th., 1900, xxx, 883.
[14] Sabrazes. Journal of the Chemical Society, 1898, 74–2, p. 35.
[15] Andrew. Journal of the American Medical Association, 1885, v, 177.
[16] Oppenheim r. "Die Fermente und ihre Wirkung," Leipzig, 1900.
[17] Pavy. "Physiology of the Carbohydrates," London, 1894.
[18] Bing. Jahrsb. Th., 1898, xxviii, p. 164.
[19] Bing. Jahrsb. Th., 1899, xxix, p. 187.
[20] Henriques. Jahrsb. Th., 1897, xxvii, p. 47.